# Risk of Malignancy (ROM) in the Various Categories of the UK Royal College of Pathologists Thy Terminology for Thyroid FNAC Cytology: A Systematic Review and Meta-analysis.

**RUNNING TITLE:** Risk of Malignancy in the UK Thyroid Cytology Terminology: A Meta-analysis.

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## Abstract

**Background.** The UK Royal College of Pathologists Thy terminology for reporting thyroid FNAC cytology was first published in 2009, used throughout the United Kingdom and Ireland, in some parts of Italy and Switzerland, and elsewhere. There is no review of the literature or meta-analysis of the risk of malignancy (ROM) in the various categories of the UK Thy terminology. The study goal was to establish the published ROM for each Thy category and compare results with other existing terminology systems where similar meta-analyses were available.

**Methods.** A comprehensive literature search of online databases was conducted in May 2019 examining the ROM for histologically proven nodules with preoperative FNAC classified according to the UK Thy terminology.

**Results.** 25 articles were identified showing results of both cytology and histology. 12 of these were excluded to prevent selection bias as they showed data in just one Thy category. In the remaining 13 articles the pooled ROM was as follows; Thy 1: 12% (± 5-22%;95% CI); Thy 2: 5% (± 3-9%;95% CI); Thy 3: 22% (± 18-26%;95% CI); Thy 3a: 25% (± 20-31%;95% CI); Thy 3f: 31% (± 24-39%;95% CI); Thy 4: 79% (± 70-87%;95% CI); and Thy 5: 98% (± 97-99%; 95% CI) .

**Conclusion.** This meta-analysis shows comparable results to meta-analyses of other internationally recognised reporting terminologies for pooled risk of malignancy for surgically excised nodules in the various Thy reporting categories. There is comparatively little difference (6% only) between the pooled ROM of Thy 3a and Thy 3f surgically excised nodules.

## Introduction

The UK *Thy* terminology for reporting thyroid FNAC cytology was developed in response to the need for a standardised reporting terminology for fine-needle aspiration cytology (FNAC), to improve clinical management of patients. The first major internationally recognised system for reporting thyroid FNAC was the 1996 Papanicolaou Society Guideline [1]. Subsequently, in the UK Newcastle [2] and Portsmouth [3] separately published tiered classification systems for in-house reporting of thyroid FNAC, followed in 2002 by national guidance from The British Thyroid Association (BTA) and The Royal College of Physicians of London, *Guidelines for the Management of Thyroid Cancer in Adults* [4], a second edition in 2007 [5] and a third edition in 2014 [6]. After the 2007 Bethesda National Cancer Institute Thyroid Fine Needle Aspiration (FNAC) State of the Science Conference [7] in 2009 The UK Royal College of Pathologists (RCPath) published the first edition of the *Thy* terminology [8] and this was revised in 2016 [9]. The current 2016 RCPath guidance has five major categories, dividing the indeterminate category '*neoplasm possible-Thy 3*' into *Thy 3a* (neoplasm possible – atypia / non-diagnostic) and *Thy 3f* (neoplasm possible, suggestive of follicular neoplasm) [9]. There is also a separate category for thyroid cysts, *Thy 1c*. The RCPath guidance aligns with The Bethesda System for Reporting Thyroid Cytology (TBSRTC) and other international reporting systems for reporting thyroid FNAC cytology, see table 1.

The purpose of this meta-analysis was to review the peer-reviewed published literature to date to examine the stated rate(s) or risk(s) of malignancy (ROM) for patients undergoing thyroid surgery and reported using the UK *Thy* terminology in the various *Thy* categories.

## Material and Methods

*Conduct of review*

This present systematic review was conducted according to Prisma guidelines.

*Search strategy*

A comprehensive literature search was conducted using the online databases; Pubmed/MEDLINE, Scopus™ and ISI Web of Knowledge™. The search aimed to find original peer reviewed studies describing the prevalence of malignancy among nodules undergoing surgery and cytologically classified according to

the RCPath '*Thy*' system with confirmatory histopathological diagnosis. A combination of the search subject terms ('thyroid' &, 'cytology' & 'Thy') was applied. A starting date limit of 2008 was applied as the first UK national guidance was not published by RCPath until 2009 [8]. The search was updated to May 15, 2019, and no language restrictions were used. This approach identified a large number of studies; Pubmed/MEDLINE (58), Scopus™ (51) and ISI Web of Science (43)™. To expand the search, references in the retrieved articles were also screened to identify additional studies.

*Study selection*

The study inclusion criterion was peer-reviewed original articles reporting thyroid nodules undergoing FNAC before surgery and cytologically classified according to either the first [8] or second editions [9] of The RCPath Guidance on the Reporting of Thyroid Cytology Specimens with histological diagnosis information included in the reports. Two researchers (DP and MB) independently reviewed the titles and abstracts of the retrieved articles, applying the study selection criteria and then all authors independently reviewed the full-text of the remaining articles. Articles or audits available online but not published in peer-reviewed journals were excluded including studies describing the histological outcome(s) of two subcategories in the same group e.g. *Thy 3* & *Thy 3a* or *Thy 3, Thy 3a,* and *Thy 3f*. Studies reporting patients undergoing surgery in only one diagnostic grouping, the indeterminate category, '*neoplasm possible-Thy3'* diagnosis (*Thy3, Thy3a, Thy3f*) were also excluded to avoid potential selection bias as these patients are typically selected for surgery based on local institutional and clinical management preferences. Articles with less than fifty patients were also excluded as were articles with overlapping patient or nodule data, and case reports were not considered.

*Data extraction*

For each included study, the following information was extracted independently in a piloted form: 1) study data (authors, year and journal of publication, country of origin); 2) study period; 3) number of cases in any *Thy* category; 4) number of cancers in any RCPath *Thy* category. Data were cross-checked, and any discrepancies were discussed and mutually resolved.

*Study quality assessment*

The risk of bias of included studies was assessed independently by two reviewers (DP, PT) through the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool for the following aspects: patient selection; index test; reference standard; flow and timing. Risk of bias and concerns about applicability were rated as low, high and unclear risk.

*Statistical analysis*

A proportion meta-analysis was performed to obtain the pooled rate of histologically proven cancer among all nodules within a specific FNAC class. If in a specific analysis there was one study with a single nodule, that study was excluded from that specific analysis. For statistical pooling of data, the DerSimonian and Laird method (random-effects model) was used [10]. In this model, pooled data represent weighted averages related to the sample sizes of studies. Pooled data are presented with 95% confidence intervals (95% CI) and displayed using a Forest plot. The I-square index was used to quantify the heterogeneity among the studies, and significant heterogeneity was defined as an I-square value > 50%. Egger's test was carried out to evaluate the possible presence of significant publication bias. Significance was set at $p<0.05$. Statistical analyses were performed using the StatsDirect statistical software (StatsDirect Ltd; Altrincham, UK).

**Results**

*Qualitative analysis (systematic review)*

According to the above search algorithm, 25 articles were selected among the total retrieved online. Out of 25 articles, 12 were excluded because they reported data in one single RCPath '*Thy'* terminology category; Alexander [11], Mihai [12], Tysome [13], Dutta [14], Lakhani [15], Pagni [16], Wong [17], Rago [18], Brophy [19], Trombetta [20], Giusti [21], Khalil [22]. Finally, 13 articles; Agrawal [23], Dallari [24], Deandrea [25], Doddi [26], Fadda [27], Gill [28], Glynn [29], Kelly [30], Lobo [31], Mehanna [32], Montgomery [33], Mullen [34] and Parkinson [35] were included in the present systematic review and meta-analysis. These 13 studies describe a total of 3910 nodules with histological diagnosis and preoperative FNAC assessment according to The RCPath *Thy* terminology.

*Study quality assessment*

Quality assessment of the studies is reported in Table 2. Overall, all studies enrolled consecutive patients with thyroid nodules. Of note only one study did not state the study period. Importantly, regarding the reference standard (histological diagnosis), there was low risk in all studies.

*Quantitative analysis (meta-analysis)*

The 13 articles included in the meta-analysis report the histological outcome of 3910 nodules with preoperative FNAC classified according to The RCPath *Thy* terminology. Of note there were 598 *Thy 1*, 1351 *Thy 2*, 625 *Thy 3*, 236 *Thy 3a*, 376 *Thy 3f*, 319 *Thy 4*, and 406 *Thy 5*. Table 3 details data in the included 13 articles. As a consequence, it was possible to perform a meta-analysis of all RCPath *Thy* terminology classes except for *Thy 1c* due to absence of data. Importantly, there are studies reporting data for the indeterminate cytological category as a whole (*Thy3*) and managed by surgery and there are other studies reporting data for *Thy 3a* and *Thy 3f* separately. In the meta-analysis of *Thy 4*, the single case in the study by Kelly et al. [30] was excluded to avoid bias. Unfortunately, it was not possible to perform a meta-analysis of the differing histological subtypes of carcinoma (i.e., papillary, follicular, medullary, anaplastic) due to insufficient data. The pooled ROM of the cytological categories was following: 12% in *Thy 1*, 5% in *Thy 2*, 22% in *Thy 3*, 25% in *Thy 3a*, 31% in *Thy 3f*, 79% in *Thy 4*, 98% in *Thy 5*. The most statistically powerful results were those for *Thy 3a*, and *Thy 5* which showed absence of heterogeneity. Results for *Thy 1*, *Thy 2*, and *Thy 3* showed significant publication bias. Table 4 details the general results.

**Discussion**

The published literature in thyroid FNAC cytology is heterogeneous, and many studies report series of cytology cases but without the accompanying histology. In the 13 articles included in this meta-analysis the ROM in the various cytological subcategories were as follows; Thy 1 12% (± 5-22%;95% CI), Thy 2 5% (± 3-9%;95% CI), Thy 3 22% (± 18-26%;95% CI), Thy 3a 25% (± 20-31%;95% CI), Thy 3f 31% (± 24-39%;95% CI) , Thy 4 79% (± 70-87%;95% CI) and Thy 5 98% (± 97-99%; 95% CI). This meta-analysis shows comparable results to other internationally recognised reporting terminologies for risk of malignancy for surgically excised nodules in the various reporting categories. Without taking account of NIFTP tumours the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) shows a ROM for non-diagnostic/unsatisfactory FNAC of 5-10% which is equivalent to Thy 1, for TBSRTC benign 0-3% equivalent to Thy 2, for TBSRTC atypia of undetermined significance/follicular lesion of undetermined significance ~10-30% equivalent to Thy 3a, for TBSRTC follicular neoplasm/suspicious for a follicular neoplasm 20-40 %, equivalent to Thy 3f, for TBSRTC suspicious for malignancy 50-75%, equivalent to Thy 4 and for TBSRTC malignant 97-99%, equivalent to Thy5 [36]. The reason for the relatively higher rates of malignancy in the lower risk groups, Thy 1 (12%) and Thy 2 (5%) is because this meta-analysis is biased by the fact that only patients undergoing surgery were included in the analysis.

There is comparatively little difference (6%) in ROM of Thy 3a (25%) and Thy 3f (31%) surgically excised nodules. The ROM for Thy 3a FNAC (25%) lies within with the range of ~10-30% seen for TBSRTC atypia of undetermined significance/follicular lesion of undetermined significance and the ROM of Thy 3f (31%) also lies within the range expected in the Bethesda terminology of 25 to 40% for TBSRTC follicular neoplasm/suspicious for a follicular neoplasm [36]. Both the UK and Bethesda terminologies include cases with atypia in both indeterminate categories, Thy 3a and Thy 3f, equivalent to TBSRTC atypia of undetermined significance/follicular lesion of undetermined significance and TBSRTC follicular neoplasm/suspicious for a follicular neoplasm respectively. This explains the similar risk of malignancy seen in the two indeterminate categories in both the UK and the Bethesda terminology. The Italian TIR system by contrast places cases with atypia in a TIR higher risk indeterminate category, category IIIB, [37] hence meta-analyses of the Italian TIR terminology show greater separation for risk of malignancy in the lower

and higher risk FNAC categories [38]. No meta-analyses of the Japanese or Australian terminologies have been undertaken to the authors' knowledge.

It should be noted that by including only patients undergoing surgery in this meta-analysis there is an inevitable bias towards higher rates of malignancy as higher rates of malignancy are seen in patients undergoing surgery for thyroid nodules with concerning clinical features; for example clinically or suspicious features on ultrasound, patient or clinician preference. This series is therefore risk-biased as it does not include patients that have not undergone thyroid surgery who would be expected to have lower ROM's for thyroid nodules that did not undergo surgery.

The published data presented here shows that the UK system is comparable to other terminologies for reporting FNAC cytology as it is particularly aligned with the TBSRTC on which it was partially modelled as the UK terminology was published shortly after the Bethesda thyroid FNAC cytology state of the science conference in 2009. The only major difference between the UK system and the Bethesda system is a separate subcategory for cystic lesions, Thy 1c, although this study was unable to identify the effect of Thy 1c aspirates due to low numbers of cases and lack of surgical pathology correlation. Of the terminology systems in use in Europe the Italian system gives greater separation of the subcategories in indeterminate categories TIR 3A & TIR 3B [36].

The introduction of NIFTP terminology in 2016 and its incorporation into the World Health Organization Classification of Tumours of Endocrine Organs in 2017 [39] would be expected to reduce the risk of overdiagnosis of encapsulated follicular variant of papillary thyroid carcinoma [40]. In some areas of the world pre-2016 the rate of diagnosis of encapsulated follicular variant of papillary thyroid carcinoma was extremely high [39] although in the UK this was a comparatively rare [41] diagnosis. TBSRTC in 2017 adopted NIFTP terminology and provided two ranges of risk of malignancy, one which considers NIFTP as a malignant tumour the other which does not [36]. All the studies included in this meta-analysis predate introduction of NIFTP terminology and hence the issue of NI FTP was not discussed in any of the published articles included in this analysis. The limitations of the study are that it does not include nonoperated patients, and only 6 of the 12 studies included are from the UK itself with a further 4 from Ireland. One

aspect that this analysis makes clear is that there is no over-arching national registry for thyroid nodules in the UK or elsewhere to the authors' knowledge, and systems for data collectionfor thyroid nodule and thyroid cancer patients require further development. This study confirms the validity and clinical applicability of the UK Thy terminology system.

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**Table 1 Internationally used terminology systems for Thyroid FNAC Cytology**

| RCPath | Bethesda | Italian | Australian | Japanese |
|---|---|---|---|---|
| **Thy1**<br>Non-diagnostic for cytological diagnosis<br><br>**Thy1c**<br>Non-diagnostic for cytological diagnosis – cystic lesion | **I**.<br>Non-diagnostic or unsatisfactory | **TIR 1**<br>Non-diagnostic<br><br>**TIR 1c**<br>Non-diagnostic cystic | 1<br>Non-diagnostic | 1<br>Inadequate |
| **Thy2**<br>Non-neoplastic<br><br>**Thy2c**<br>Non-neoplastic – cystic lesion | **II**.<br>Benign | **TIR 2**<br>Non-malignant | 2<br>Benign | 2<br>Normal or benign |
| **Thy3a**<br>Neoplasm possible – atypia / non-diagnostic | **III**.<br>Atypia of undetermined significance or follicular lesion of undetermined significance | **TIR 3A**<br>Low risk indeterminate lesion (LRIL) | 3<br>Indeterminate or follicular lesion of undetermined significance | 3 Indeterminate<br>B others |
| **Thy3f**<br>Neoplasm possible, suggesting follicular neoplasm | **IV**.<br>Follicular neoplasm or suspicious for a follicular neoplasm | **TIR 3B**<br>High risk indeterminate lesion (HRIL) | 4<br>Suggestive of a follicular neoplasm | 3 Indeterminate<br>A follicular neoplasms<br>A-1 favor benign<br>A-2 borderline<br>A-3 favor malignant |
| **Thy4**<br>Suspicious of malignancy | **V**.<br>Suspicious for malignancy | **TIR 4**<br>Suspicious of malignancy | 5<br>Suspicious of malignancy | 4<br>Malignancy suspected |
| **Thy5**<br>Malignant | **VI**.<br>Malignant | **TIR 5**<br>Malignant | 6<br>Malignant | 5<br>Malignancy |

Table 2. Quality assessment of the studies according to QUADAS-2.

| | Risk of bias | | | | Feasibility | | |
|---|---|---|---|---|---|---|---|
| First author (ref) | Patients selection | Index test | Reference standard | Flow and timing | Patients selection | Index test | Reference standard |
| Agrawal | L | L | L | L | L | L | L |
| Dallari | U | U | L | L | L | L | L |
| Deandrea | U | L | L | L | L | L | L |
| Doddi | L | L | L | L | L | L | L |
| Fadda | U | L | L | L | U | L | L |
| Gill | H | L | L | H | H | L | L |
| Glynn | L | L | L | L | L | L | L |
| Kelly | L | U | L | L | L | L | L |
| Lobo | L | L | L | L | L | L | L |
| Mehanna | L | L | L | L | L | L | L |
| Montgomery | H | L | L | L | H | L | L |
| Mullen | L | L | L | L | L | L | L |
| Parkinson | L | L | L | L | L | L | L |

Legend – The risk of bias was assessed as low (L), high (H), or unclear (U).

**Table 3. Data retrieved in the studies included in the systematic review.**

| First author (ref) | Thy1 | Thy2 | Thy3 | Thy3a | Thy3f | Thy4 | Thy5 |
|---|---|---|---|---|---|---|---|
| Agrawal | - | 174 | 7 | - | - | 4 | 18 |
| Dallari | - | 29 | 33 | - | - | 7 | 18 |
| Deandrea | 51 | 319 | 294 | - | - | 91 | 172 |
| Doddi | 269 | 287 | 48 | - | - | 11 | 6 |
| Fadda | - | 8 | 50 | - | - | 59 | 3 |
| Gill | 93 | 78 | - | 67 | 88 | - | - |
| Glynn | 16 | 30 | 55 | - | - | 8 | 9 |
| Kelly | - | 79 | 21 | - | - | 1 | 5 |
| Lobo | - | - | - | 10 | 72 | 11 | 43 |
| Mehanna | 28 | 88 | 117 | - | - | - | - |
| Montgomery | - | - | - | - | - | 40 | 25 |
| Mullen | - | 80 | - | 7 | 52 | 21 | 36 |
| Parkinson | 141 | 179 | - | 152 | 164 | 66 | 71 |

**Table 4. Results of the meta-analyses.**

| | Cancer prevalence (95% CI) | Consistency – I2 (95% CI) | Egger test (p) |
|---|---|---|---|
| Thy1 | 12 (5 to 22) | 88.7% (77.2 to 93.1) | 0.025 |
| Thy2 | 5 (3 to 9) | 80.7% (64.2 to 87.7) | 0.005 |
| Thy3 | 22 (18 to 26) | 27.8% (0 to 67.5) | 0.011 |
| Thy3a | 25 (20 to 31) | 0% (0 to 67.9) | 0.896 |
| Thy3f | 31 (24 to 39) | 59% (0 to 84.3) | 0.790 |
| Thy4 | 79 (70 to 87) | 65.5% (16 to 80.8) | 0.365 |
| Thy5 | 98 (97 to 99) | 0% (0 to 51.2) | 0.321 |